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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,252	CERIANI ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-87* is/are pending in the application.

4a) Of the above claim(s) *65-80 and 85-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/02/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group II, claim 61 in paper of 10/03, 2003 is acknowledged and entered.

Applicant cancels claims 52-64 and adds new claims 65-87.

Since applicant has elected Group II, an in vivo method for imaging a neoplasia of epithelial origin, using a monoclonal antibody specific for the 46 Kd human milk fat globule (HMFG) differentiation antigen, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of 1) Claims 65-79, drawn to a specifically targeted antibody, comprising a monoclonal antibody specific for the 46 Kd human milk fat globule (HMFG) differentiation antigen, 2) Claims 85-87, drawn to an in vivo or ex vivo method for delivering a therapeutic agent to target neoplastic cells of epithelial origin, have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03. Newly submitted claims 65-79 and 85-87 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

1) The method of the elected invention is distinct from the antibodies of claims 65-67 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (i) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* §

806.05(h)]. In the instant case the antibody product as claimed can be used in a materially different process such as affinity chromatography.

2) The method of the elected invention is distinct from the methods of claims 85-87 at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 81-84 are examined in the instant application.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

1) It is not clear which polypeptides and polynucleotides recited in the specification correspond to the sequences listed in the sequence listings.

2) Tables 1, 2, on pages 50, 52, respectively, recite sequences without sequence identification numbers.

OBJECTION

1. Claim 81 is objected for depending on non-elected claim 65.

2. Claims 81-84 are objected to for the use of the language the 46 kD human milk fat globule (HMFG) differentiation antigen as the sole means of identifying the claimed

antigen. Different laboratories may use the same laboratory designations to define completely distinct antigens. Amendment of the claims to include physical and/or functional characteristics of the 46 kD human milk fat globule (HMFG) differentiation antigen which unambiguously define the 46 kD human milk fat globule (HMFG) differentiation antigen is required.

3. Claims 81-84 are objected to for the use of the language "the unlabeled agent" of claim 65, which lacks antecedent basis.

4. Claims 81-84 are objected to because it is not clear in claim 81 whether the administered labeled agent of claim 65 is referred to the detectable label agent per se or to the labeled monoclonal antibody.

For the purpose of compact prosecution, it is assumed that the labeled or unlabeled agent of claim 65 refers to the labeled or unlabeled monoclonal antibody of claim 65.

5. Claims 81-84 are objected to, for the use of the language detecting "any" label in the subject's body in claim 81. It is not clear which label is referred to.

For the purpose of compact prosecution, it is assumed that detecting the presence of any label of claim 81 refers to detecting the presence of the labeled agent that binding the antibody of claim 65.

6. Claims 81-85 are objected to for the use of the language "preferentially" in claim 81, because it is not clear that the antibody is preferentially delivered to the target neoplastic cells as compared to what?

7. The amendment in the specification on pages 20, 21 changing the size of the amino acids is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant is required to cancel the new matter in the response to this Office action.

8. The figure is objected to because it is not clear which of the recited breast cell lines are normal breast cell lines and which of the recited breast cell lines are cancerous breast cell lines.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER

Claims 81-84 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation "neoplasia" of epithelial origin of Claims 81-84 has no clear support in the specification and the claims as originally filed.

A review of the specification provides support for a) a desire for detection, diagnosis of breast cancer (p.16, paragraph under best mode for carrying out the invention, b) a method for determining the presence of epithelial cells (p.25, paragraph before last), and c) an in vivo method for imaging cells expressing a polypeptide having the antibody binding specificity of the about 46 kDa differentiation of the HMFG system (p.26, last paragraph).

The subject matter claimed in claims 81-84 broadens the scope of the invention as originally disclosed in the specification.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims **81-83** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description inquiry, *whatever is now claimed*. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 81-83 are drawn to an in vivo method for imaging a neoplasia of epithelial origin, comprising

administering to a subject a labeled or unlabeled monoclonal antibody selectively binding the 46 Kd MW human milk fat globule (HMFG) differentiation antigen, which has an affinity constant for the antigen of about 10^{10} to 10^{5} M^{-1}, linked to an agent comprising an immunotoxin or a detectable label, to deliver it to preferentially to target neoplastic cells of epithelial origin,

administering to the subject a detectable labeled "agent" binding the antibody at a site other than the binding site for the 46 kD HMFG polypeptide; and

detecting the presence of any label in the subject body.

It is noted that a labeled agent binding to the 46 kDa HMFG encompasses an compound with diverse structure, wherein said agent binds to the 46 kDa HMFG.

It is further noted that the specification only discloses a single species of labeled agent that binds to the 46 kDa HMFG, i.e. a labeled anti-antibody immunoglobulin (p.27, last paragraph, bridging p.28).

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that An adequate written description of a DNA... requires a precise

definition, such as by structure, formula, chemical name, or physical properties , not a mere wish or plan for obtaining the claimed chemical invention .

The claims, as written, however, encompass an in vivo method for imaging a neplasia of epithelial origin, using a detectable labeled "agent" binding the antibody at a site other than the binding site for the 46 kD HMFG polypeptide, the structure of which agent is not disclosed and is not necessarily similar to that of an antibody. There is no common structural attributes among the claimed labeled agent, which includes besides an anti-antibody immunoglobulin, mimetics, and small molecules.

The instant disclosure of a single species of an anti-antibody immunoglobulin, does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera having diverse structure.

The instant specification fails to provide sufficient descriptive information, such as definitive structural features of the claimed genus of the labeled agent. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the labeled agent encompassed and no identifying characteristic or property of the instant labeled agent is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, and further because the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus, the disclosure of a single anti-antibody immunoglobulin is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Thus, only an in vivo method for imaging a neplasia of epithelial origin, using a detectable labeled "anti-antibody immuglobulin" binding the antibody at a site other than the binding site for the 46 kD HMFG polypeptide, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 81-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. Claims 81-84 are rejected under 35 USC 112, first paragraph, for **lack of enablement for a method for in vivo imaging of a neoplasia of epithelial origin.**

Claims 81-84 are drawn to an in vivo method for imaging a neplasia of epithelial origin, comprising

administering to a subject a labeled or unlabeled monoclonal antibody selectively binding the 46 Kd MW human milk fat globule (HMFG) differentiation antigen, which has an affinity constant for the antigen of about 10^{10} to 10^{5} M^{-1}, linked to an agent comprising an immunotoxin or a detectable label, to deliver it to preferentially to target neoplastic cells of epithelial origin,

administering to the subject a detectable labeled agent binding the antibody at a site other than the binding site for the 46 kD HMFG polypeptide; and

detecting the presence of any label in the subject body.

The specification discloses polyclonal antibodies that identify the 150 kDa, 70 kDa and 46 KDa HMFG have high specificity for normal breast epithelial cells and breast carcinomas (p.2, second paragraph). The specification discloses that monoclonal antibodies have been prepared against the 70 kDa and 46 kDa components of the HMFG (lines 27-29). The specification discloses that the 70 KDa and 46 kDa component of HMFG are found in the serum of breast cancer patients and thus can be used as markers for breast cancer in serum assay (p.3, last two paragraphs).

The specification further discloses that some monoclonal antibodies against the 46 kDa HMFG do not stain normal breast tissue, but weakly stain breast carcinomas (p.18, second paragraph, especially lines 13-15).

It is noted that no data is shown concerning overexpression of the 46 kDa HMFG in breast cancer tissue in vivo, as compared to normal breast tissue as detected by monoclonal antibodies specific for said 46 kDa HMFG.

The specification further discloses that breast carcinoma cell lines have high level of the mRNA for this 46 kDa antigen (p.18, lines 16-34, and figure 1).

One cannot extrapolate the teaching in the specification to the enablement of the claims, because in the absence of objective evidence, one cannot determine whether the 46 kDa HMFG could be detected in vivo imaging in breast cancer tissue, as compared to normal breast tissue, as detected by monoclonal antibodies specific for said 46 kDa HMFG, especially in view of the disclosure in the specification that polyclonal antibodies that identify the 150 kDa, 70 kDa and 46 KDa HMFG have high specificity for both normal breast epithelial cells and breast carcinomas (specification, p.2, second paragraph), and that some monoclonal antibodies against the 46 Kda HMFG, although do not stain normal breast tissues, only weakly stain breast carcinomas (p.18, lines 12-15). This is confirmed by Peterson et al, 1990, Hybridoma, 9(3): 221-235, which teaches that monoclonal antibodies Mc3 and Mc8 to the 46 kDa HMFG only weakly stains breast carcinomas by immunohistochemistry, indicating that this antigen is too low in density (table 4 on page 228 and p.230, third paragraph), while breast cancer cell lines have significant amount of the 46 kDa HMFG (table 6).

In other words, the 46 kDa HMFG antigen is too low in density in breast carcinoma tissues, and it is unpredictable that the 46 kDa HMFG antigen is suitable for use in in vivo imaging of epithelial or breast cancer. The following teaching of White et

al, 2001, Ann Rev Med, 52: 125-145, although drawn to immunotherapy, applies as well to in vivo imaging of the claimed invention, because besides the specificity of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause invivo imaging to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Thus in view of the teaching in the art, one cannot predict that the 46 kDa protein would have properties suitable for in vivo imaging of breast cancer cells or of epithelial cancer cells.

Moreover, although Peterson et al, 1990, supra, speculates that possible explanation for the low density of the 46 kDa protein in immunohistopathology is that the 46 kDa protein antigen could be destroyed by fixation, or are washed off the cells in the fixation and staining procedure (p.230, third paragraph), however, one cannot predict that the inherent number of the 46 kDa antigens in breast carcinoma tissues is significant, in view that expression level of a protein in a cell line in culture cannot be predictably correlated with its level in cancer tissue in vivo, due to culture artifact. It is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during

adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Thus in view of the teaching in the art, one cannot predict that the density of the 46 kDa protein would be adequate in breast cancer tissue.

Moreover, the outcome of claimed in vivo imaging is further unpredicted by the fact that the serum of patients with breast carcinoma has a significant level of the 46 kDa human milk fat globule, as detected by monoclonal antibodies (Salinas, F et al, 1987, Cancer Res, 47: 907-913, and Ceriani RL et al, 1983, Somatic cell genet, 9: 415-

427). In other words, since the level of the 46 kDa human milk fat globule is significantly, and the level of said 46 kDa protein is very weak on cancer cell surface, one cannot predict whether most of the administered monoclonal antibodies would not be absorbed by the the 46 kDa human milk fat globule in serum, and whether the amount of the monoclonal antibodies reaching the breast cancer tissues would be adequate for imaging the 46 kDa human milk fat globule, especially when said 46 kDa protein could be present in too low in density in breast carcinoma tissues. The specification however does not disclose the necessary dosage of the administered monoclonal antibodies, such that the claimed method is effective as claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. If Applicant could overcome the above 112, first paragraph, claims 81-84 are still rejected under 112, first paragraph, because **claims 81-84 encompass a method for in vivo imaging any cancer or any growth which is not necessarily cancer of any epithelial cells, which are not necessarily breast cells.**

It is noted that neoplasm encompasses any abnormal formation of tissue, as a tumor or growth, and is not necessarily cancerous growth, for example, a benign tumor, a histoid, a multicentric, or an organoid (Taber's cyclopedic medical dictionary, 16th ed, 1989, pages 1190-1191).

One cannot extrapolate the teaching of the specification to the scope of the claims because different diseases have different etiology, and expression of a gene in certain diseases is unrelated to its expression in other diseases, and thus it is

unpredictable that over-expression of the 46 kDa HMFG is found in a neoplasm of epithelial origin, such as a benign tumor, a histoid, a multicentric, or an organoid. Further, different cancers have different etiology and characteristics, and mutation or amplification of a gene in a specific cancer is not necessarily the same as that for the same gene in another type of cancer. For example, Montesano, R et al,1996, Intl J Cancer, 69(3): 225-235, teach that two different forms of esophagus cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) have different etiological and pathological characteristics, and that a comparison of p53 mutations in these two cancers shows that said mutations differ by their types, frequencies, distribution along the gene and impact on p53 protein structure (p.231, second column, first paragraph). Similarly, Burmer, GC et al, 1991, Environmental Health perspectives, 93: 27-31, teach that in contrast to sporadic colon carcinomas, mutations in c-Ki-ras are infrequently observed in carcinomas or areas of high-grade dysplasia in patients with chronic ulcerative colitis, and that differences in the frequency, and spectrum of mutations observed in sporadic colon carcinoma and pancreatic carcinoma suggest that a different class of carcinogens may be involved in the initiation of these two tumors (p.27, second column, last paragraph, bridging p.28). Busken, C et al, Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850, teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of

the abstract). Thus based on the teaching in the art and in the specification, one cannot predict that the 46 kDa HMFG is amplified in neoplasia of epithelial origin.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph, claims 81-84 are still rejected under 112, first paragraph, because **claims 81-84 encompass a method for in vivo imaging a neoplasia of epithelial origin, using a monoclonal antibody that selectively binds to the 46 KDa HMFG differentiation antigen, which is linked to an immunotoxin.**

One cannot extrapolate the teaching in the specification to the scope of the claims, because it is well known in the art that the purpose of an immunotoxin is for killing a cell, and not for diagnosis purpose.

The specification does not disclose how to detect a neoplasia of epithelial origin, using a monoclonal antibody that selectively binds to the 46 KDa HMFG which is linked to an immunotoxin.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

D. If Applicant could overcome the above 112, first paragraph, claims 81-83 are still rejected under 112, first paragraph, because **claims 81-83 encompass a method for in vivo imaging using any labeled agent with any structure that binds to the monoclonal antibody specific for the 46 kDa HMFG differentiation antigen.**

Applicant has not taught how to make numerous labeled agents that binds to the antibody specific for the 46 kDa HMFG. It is noted that there is no disclosure concerning the configuration of the site on the antibody specific for the 46 kDa HMFG to which the labeled agent bind. There is no disclosure of how to make the mimetics or small molecule binding agent. it is well known in the art that a specific binding of a ligand to a substrate requires specific interaction between the ligand and the substrate, and correct conformation of the ligand to fit into the binding site of the substrate, e.g. specific binding between a ligand and a receptor, or between an antigen and an antibody.

In addition, it is unpredictable that the claimed labeled agent, such as mimetics or small molecules could be used successfully *in vivo* for in vivo imaging of neoplasm of epithelial origin. The claimed mimetics or small molecules must accomplish several tasks to be effective. They must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the

formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CHRISTINA CHAN can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

June 16, 2004